

- Ions parallel to the z axis must be injected within an injection aperture having diameter $D = \frac{1}{2} \cdot r_0 \cdot (m/\Delta m)$.
- The maximum injection angle ψ must satisfy the condition $\tan \psi < 11.85 \cdot r_0 / L^2$.

The following general conclusions for selection can be drawn for the quality of a quadrupole mass filter from the relationships pointed out above:

The quality of a quadrupole mass filter increases with increasing rod diameter (r) and increasing rod length (L). (Fig. 20, 21)

Furthermore, with greater rod radius it is easier to fulfil the conditions for geometric accuracy (production tolerances and assignments for operating the QMS).

The quality of a quadrupole mass filter increases with increasing frequency f of the high frequency field (Fig. 22)

These considerations are offset by the larger space required for the analyzer and the lower required operating pressure and especially the necessary increased power rating of the HF generator with the corresponding effort needed.

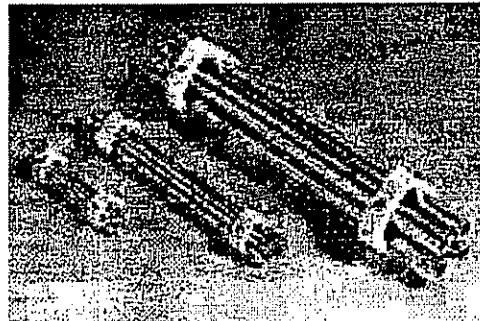


Fig. 20:
Rod systems with
diameters of 6 mm,
8 mm and 16 mm
for the analyzers
QMA 200 (QMA 125),
QMA 400 (QMA 430),
QMA 410.

The required power rating N of the HF generator is

$$\text{Power} \propto N = \text{Constant} \cdot C \cdot M_{\max} \cdot f^4 \cdot f^5$$

where C is the capacitance of the rod system including the connecting leads and M_{\max} is the maximum mass number. N increases proportional to high powers of the frequency and of the rod radius.

Fig. 20 shows the rod systems of the mass spectrometers described in this catalog.

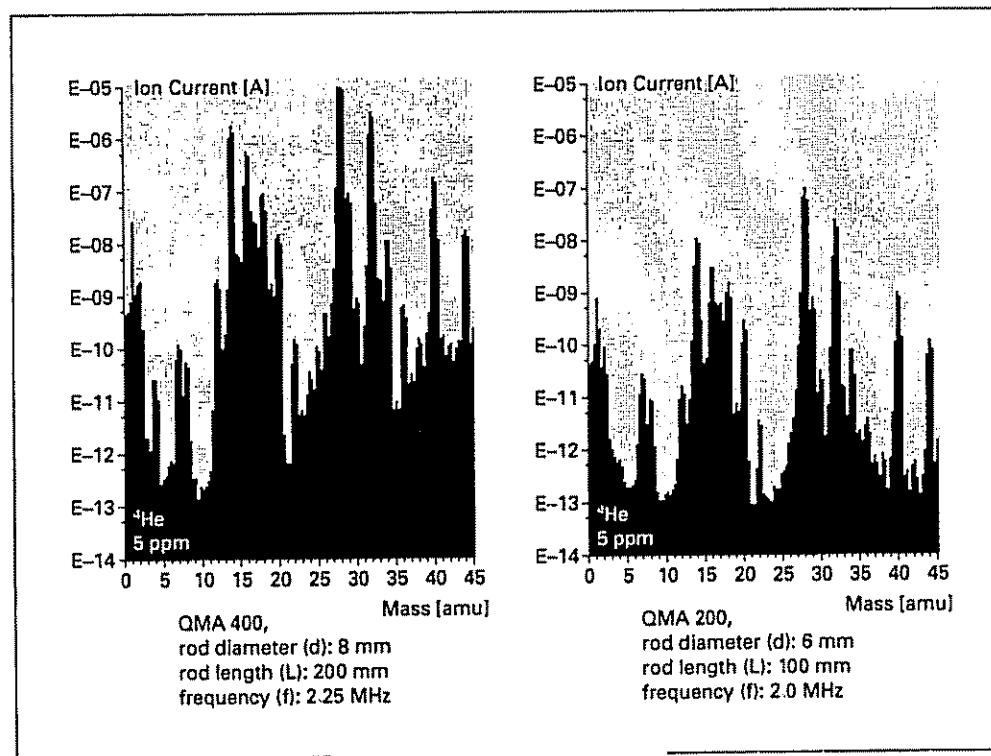
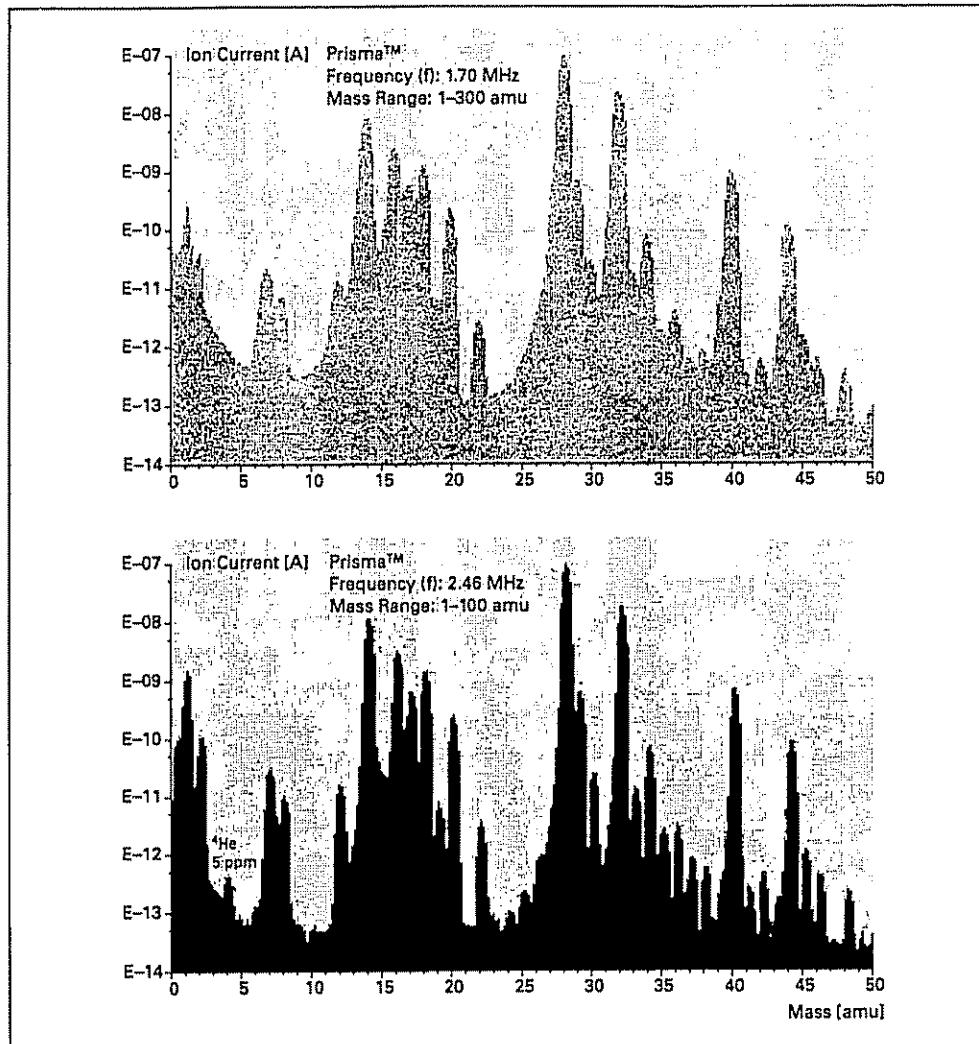


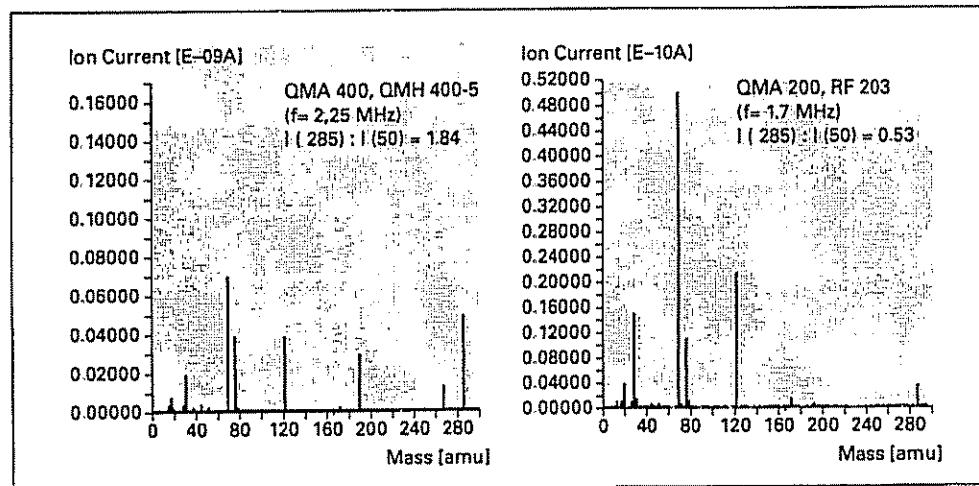
Fig. 21:
Air spectra; the input
pressure was about
 $5 \cdot 10^{-6}$ mbar in each
case.

1 Fundamentals of mass spectrometry



An other important criteria for the size of the rod system is the mass discrimination. The greater the diameter and the lenght

of the rod system, the lower is the mass discrimination. (Fig. 23)



Overview of the possible combinations of rod systems and HF generators

	Prisma™			QMG 422							
Rod diameter	6 mm	6 mm	6 mm	8 mm	8 mm	8 mm	16 mm	16 mm	16 mm	16 mm	16 mm
Rod length	100 mm	100 mm	100 mm	200 mm	200 mm	200 mm	300 mm				
Material	stainless steel	stainless steel	stainless steel	Mo							
Analyzer	QMA 200	QMA 200	QMA 200	QMA 400	QMA 400	QMA 400	QMA 410				
Mass number range	1-100	1-200	1-300	1-512	1-1024	1-2048	1-128	1-340	1-162	1-340	1-162
HF generator	RF 201	RF 202	RF 203	QMH 400-5	QMH 410-1	QMH 410-2	QMH 400-1	QMH 410-3	QMH 410-2	QMH 410-3	QMH 410-2
Frequency	2.46 MHz	2.0 MHz	2.0 MHz	2.25 MHz	2.25 MHz	1.3 MHz	2.05 MHz	1.4 MHz	2.05 MHz	1.4 MHz	2.05 MHz
Power	0.081 kVA	0.1 kVA	0.1 kVA	9 kVA	8 kVA	8 kVA	7 kVA	8 kVA	7 kVA	8 kVA	7 kVA
Contribution to adjacent mass number $^4\text{He}/5$ $^{40}\text{Ar}/41$	10 ppm	20 ppm	10 ppm	10 ppb			ppb	10	He/D reson.	possible	He/D reson.
Transmission for Xe	10%	10%	35%						50%		
Sensitivity for Ar with Faraday detector in A/mbar	$> 5 \cdot 10^{-4}$	$> 3 \cdot 10^{-4}$	$> 1 \cdot 10^{-4}$	$> 5 \cdot 10^{-4}$	$> 2 \cdot 10^{-4}$	$> 1 \cdot 10^{-4}$	$> 1 \cdot 10^{-4}$	$> 5 \cdot 10^{-4}$	$> 1 \cdot 10^{-4}$	$> 5 \cdot 10^{-4}$	$> 1 \cdot 10^{-4}$

The combination QMH 410 with QMH 402 (a modification of the QMH 400-1 for working in the so-called second stability region) is an exception. This combination has

been specially developed for analysing gas mixtures such as $^4\text{He}/\text{D}_2$, $^3\text{He}/\text{HD}$, H_3/He , $\text{CH}_3/\text{N}^{15}$ and $\text{CH}_4/\text{O}^{16}$.

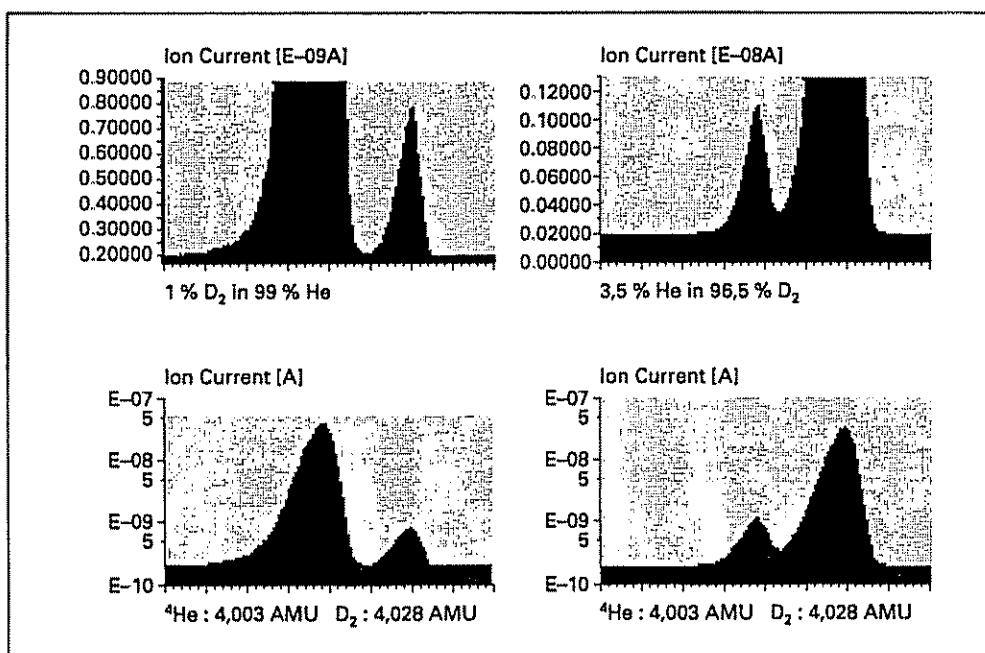


Fig. 24:
Spectra of $^4\text{He}/\text{D}_2$ gas mixtures in linear (top) and logarithmic (bottom) plot.

1 Fundamentals of mass spectrometry

1.2.3 Ion detection

The ions, which have been separated according to their mass/charge ratio in the rod system, can be electrically detected by various types of detectors:

- Faraday cup
- continuous dynode secondary electron multiplier (C-SEM) and
- discrete dynode secondary electron multiplier (SEM).

The choice of detector is primarily based on the required detection sensitivity and the detection speed. It is also determined by other application-specific requirements, such as the required stability, the thermal and chemical stability and the amount of space available.

In the simplest case, but also that with the least systematic errors, the ions hit a Faraday collector (Faraday cup) where

is therefore integrated into all analyzers described in this catalog. In combination with an electrometer preamplifier, the Faraday cup can only be used to detect positive ions.

Figure 25 shows a detector set-up with a Faraday cup and a C-SEM detector as used, e.g. in QMA 200. This C-SEM is a continuous dynode secondary electron multiplier in which the active layer has the task of multiplying the electrons as well as applied gain voltage distribution. This twin function limits the maximum current flow and the thermal stability of the continuous dynode detector. The utilizable amplification ratio of approx. 10^8 (at 2.5 kV) is essentially limited by the dark current in the active layer.

The C-SEM is positioned somewhat off the central axis of the rod system. The positive ions are deflected by applying a negative

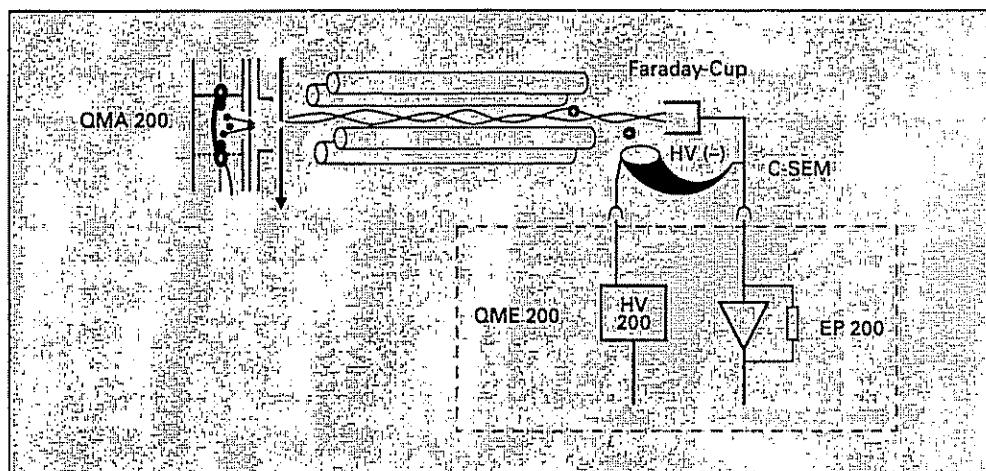


Fig. 25:
Arrangement of the
Faraday cup and C-SEM
in QMA 200.

they give up their charge. A sensitive current/voltage converter (electrometer pre-amplifier EP 422, EP 200) converts the resulting current into a voltage signal that is proportional to the ion current. The detection limit lies between $1 \cdot 10^{-16}$ – $1 \cdot 10^{-14}$ A, depending on the time constant (from a couple of seconds to 100 ms). The Faraday signal is not affected by degradation or mass-discrimination effects at the detector. In addition to the simple and robust design, a Faraday detector also has long-term stability and high thermal resistance. The Faraday cup

high voltage to the mouth of the C-SEM. The advantage of this arrangement is that it is very simple and quick to change between the two detectors. This change-over can also be carried out automatically depending on the ion current. In combination with the common electrometer pre-amplifier, the C-SEM is used to detect positive ions (from the originally neutral species) of small ion currents and rapid processes.

If there are very low ion currents and a very high measuring speed is required, the influence from photons must be reduced.

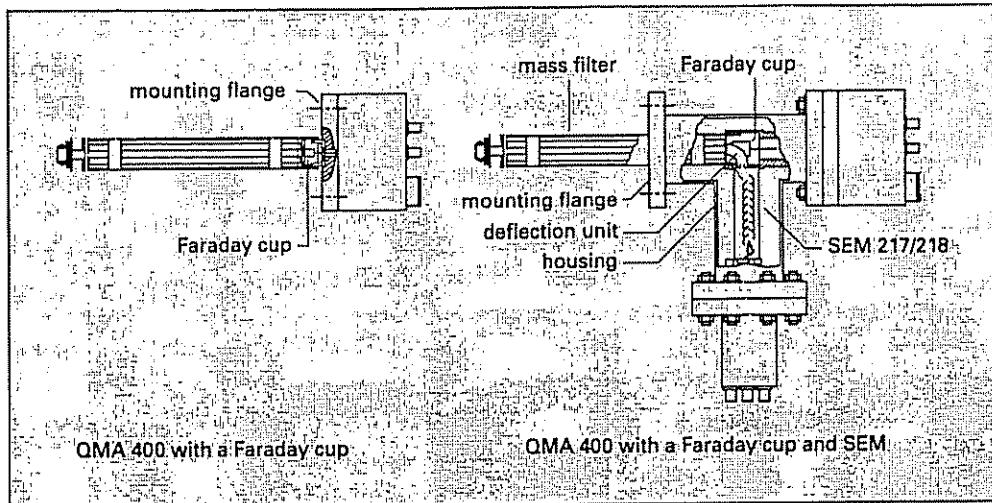


Fig. 26:
Arrangement of the
Faraday cup and
SEM 217 in QMA 400.

In this case, a discrete dynode secondary electron multiplier (SEM) is used as the detector in a 90° off-axis arrangement, as shown in Figure 26.

The ions leaving the rod system are reaccelerated to several KeV. They are then deflected so that they hit the first dynode (conversion dynode) of the SEM. Here they eject a number of electrons which are then multiplied in a series of further dynodes (16 in SEM 217, 17 in SEM 218). The

voltage for the individual dynodes is distributed via a separate resistance network. In order to minimize the contribution of impacting photons, soft x-rays or fast neutral particles (which are also coming from the direction of the rod system), the SEM is offset by 90° from the axis of the rod system. The ions are deflected by an electrostatic field which does not have any effect on uncharged particles. This produces the highest possible signal-to-noise

	C-SEM (continuous)	SEV 217 (discrete dynode)
voltage divider	continuous	1 MΩ/Dynode
amplification	10 ⁶ at 2.5 kV	10 ⁸ at 3.5 kV
arrangement	off-axis	90° off-axis
max. permissible current	10 ⁻⁶ A	10 ⁻⁵ A
max. nominal temperature range	120°C	150°C (at 1kV)
max. bakeout temperature	300°C	400°C

EXHIBIT Q


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HPLC Primer

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>> Mass Spec PrimerLC/MS - Interfacing
HPLC And MS**The Mass
Spectrometer**

The Mass Spectrometer: Instrument Architectures and Main Characteristics

In this section, we will cover the mass spectrometers which are commonly used in LC/MS configuration

Polymers Analysis

The analysers used in these instruments are quadrupole, ion trap, time of flight, and combinations such as triple quadrupoles and QTofs. We will not cover instruments like sectors, FTMS..., which are less commonly used in the LC/MS application.

Methods Validation

Amino Acid Analysis

Ion Analysis

- [Quadrupole, triple quads](#)
- [Ion Trap Analyzers](#)
- [Time of Flight \(TOF\)](#)
- [Detectors](#)

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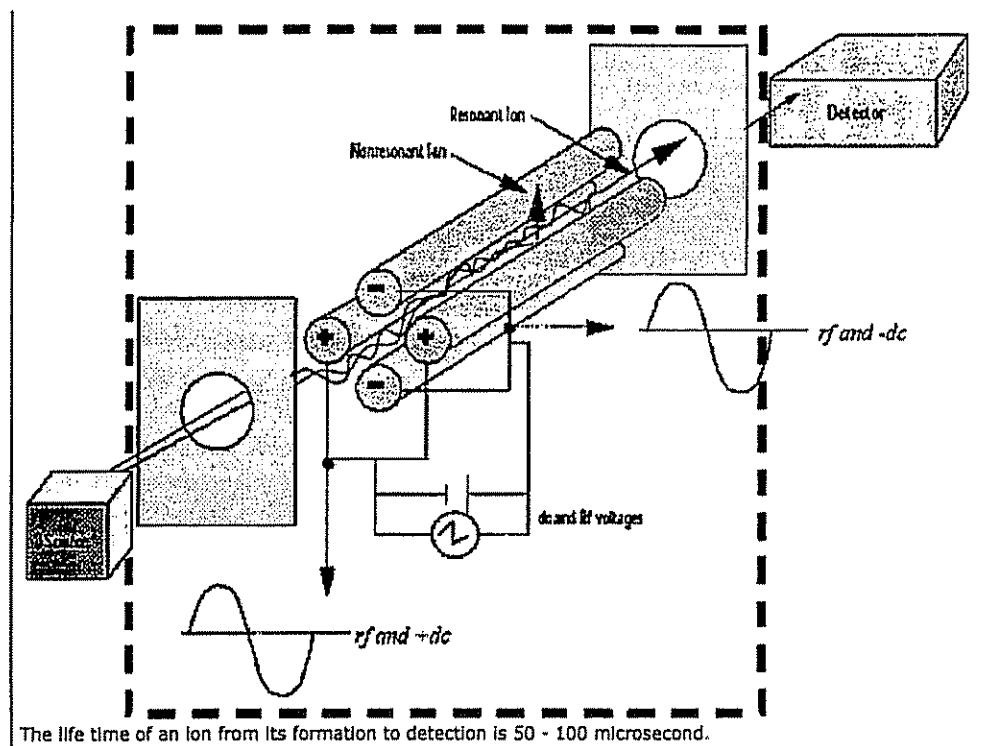
Quadrupoles, triple quads

The Quadrupole Analyzer

The quadrupole is the most widely used analyser due to its ease of use, mass range covered, good linearity for quantitative work, resolution and quality of mass spectra. All this for a relatively accessible price.

The main characteristics are:

- **Working mass range:** 10 to 4000 A.M.U.
- **Resolution:** usually operated at a resolution = 1000, but resolution can be reasonably pushed up to 4000
- **Mass accuracy:** 0.1 to 0.2 A.M.U.
- **Scan speed:** up to 5000 A.M.U per second



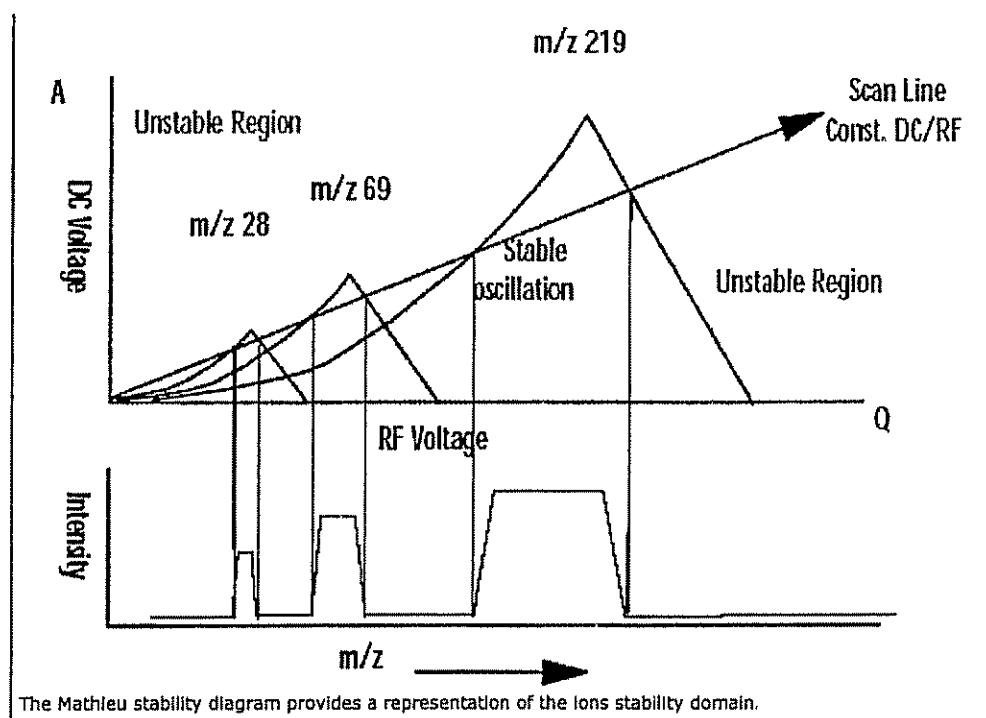
How it Works

The quadrupole is composed of two pairs of metallic rods. One set of rod is at a positive electrical potential, and the other one at a negative potential. A combination of dc and rf (radio frequency) voltages is applied on each set .

$$V(t) = -V_{dc} - V_{rf} \cos \Omega t \quad V(t) = V_{dc} + V_{rf} \cos \Omega t$$

The positive pair of rods is acting as a high mass filter, the other pair is acting as a low mass filter. The resolution depends on the dc value in relationship to the rf value. The quads are operated at constant resolution, which means that the rf/dc ratio is maintained constant.

For a given amplitude of the dc and rf voltages, only the ions of a given m/z (mass to charge) ratio will resonate, have a stable trajectory to pass the quadrupole and be detected. Other ions will be destabilized and hit the rods. The performance (i.e. ability to separate two adjacent masses across the applicable range) depends on the quad geometry, on the electronics, on the voltage settings and on the quality of the manufacturing. Increasing the resolution means that fewer ions will reach the detector, consequently impacts the sensitivity.



The quadrupole is scanned with $A/Q = \text{constant}$; the resolution depends on the slope of the scan line.

If the continuous voltage DC is switched off, the scan line is the Q axis: We have now a transfer only device like the hexapoles or octopoles used to transfer and focus the ions into the mass spectrometer optics.

SCAN and SIM

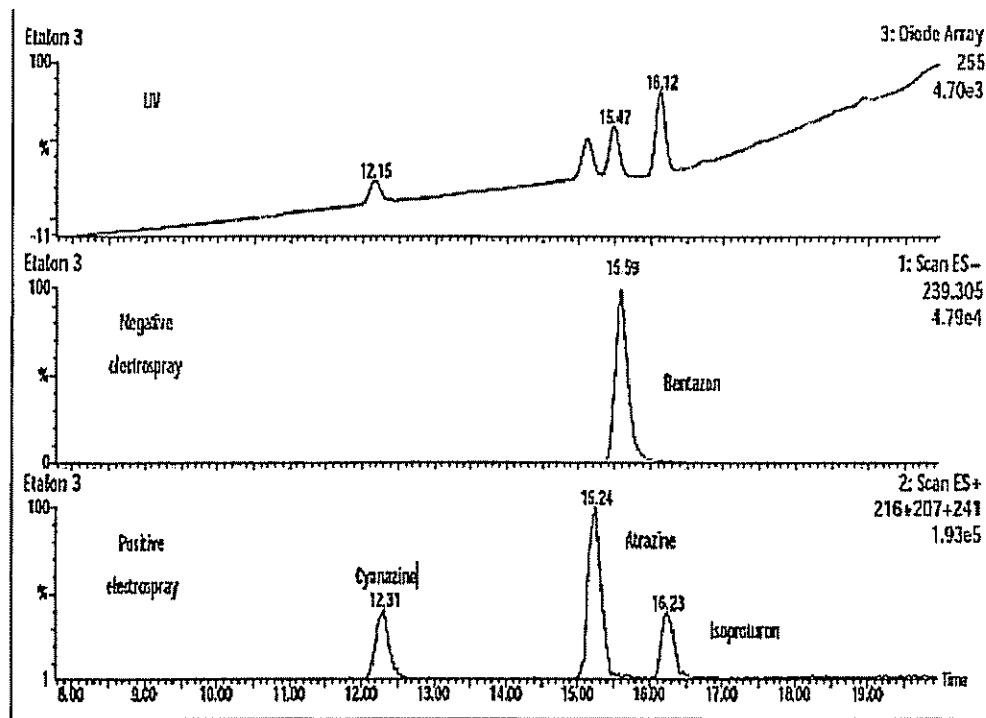
The quadrupole can be used in two modes: SIM (single ion monitoring) or Scan. The SIM mode is also called SIR (single ion recording).

In SIM mode, the parameters (amplitude of the dc and rf voltages) are set to observe only a specific mass, or a selection of specific masses. This mode provides the highest sensitivity for users interested in specific ions or fragments, since more time can be spent on each mass. That time can be adjusted; it is called the dwell time.

The mass window for observing an ion in SIM mode can be adjusted, in order to compensate small mass calibration shift. This is the span factor.

In Scan mode, the amplitude of the dc and rf voltages are ramped (while keeping a constant rf/dc ratio) to obtain the mass spectrum over the required mass range. The sensitivity is a function of the scanned mass range, scan speed, and resolution.

With most LC/MS instruments, it is possible to do positive/negative switching, in order to analyse in the same run molecules that will ionise in positive and negative modes.

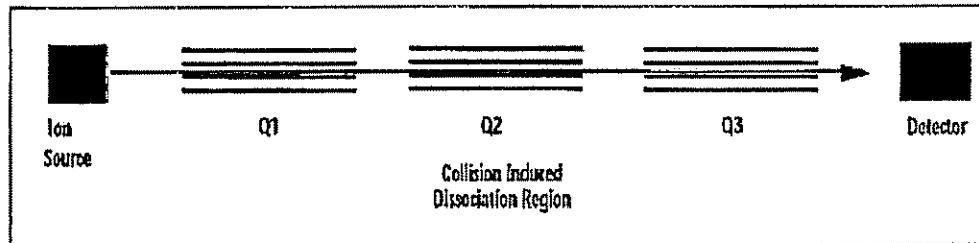


MS/MS with Triple Quadrupoles

The analyser of a "triple quad" instrument consists in two quadrupoles, separated by a collision cell. Such a configuration is often referred as a "tandem in space" instrument.

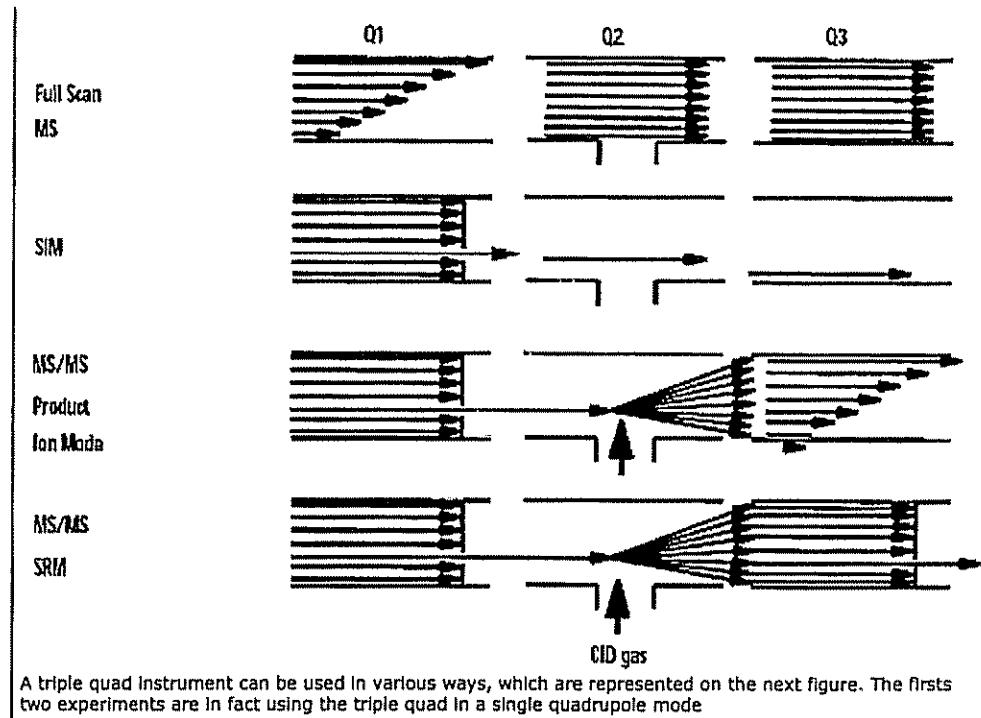
Precursor ions and product ions are created and analysed in different physical spaces.

Ions must be moved from "source" to analyser (different physical regions) where different functions take place.



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The first quadrupole is used to select a first ion (precursor), which is fragmented in the collision cell. This is typically achieved in the collision cell by accelerating the ions in the presence of a collision gas (argon, helium...).

The energy of the collision with the gas can be varied to allow different degrees of fragmentation. The resulting fragments are analysed by the second quadrupole, used either in SIM or in scan mode.

Study of mass spectral fragments can provide structural information. When using a single quadrupole instrument, it is possible to obtain fragmentation by using a technique called in source CID. The fragmentation takes place before the introduction of the ions into the optics of the mass spectrometer. This technique is useful if there is no chromatographic interference. With a triple quad system, the first quadrupole acts as a separation device, reducing the need for a perfect chromatographic separation.

The other use of a triple quad system is quantitation. The first analyser, used in SIM mode, selects the parent ion. The second analyser is also used in SIM mode to monitor a specific fragment.

Having two analysers increases the selectivity. The ion signal is reduced during the transmission, but the chemical noise, which is a major limitation for complex samples, is also largely decreased, leading to an improvement of the signal to noise ratio. It is thus possible to do quantitative analysis on complex samples like serum with a very short chromatographic separation, and even with no separation at all. This is the technique of choice for application such as pharmacology studies.

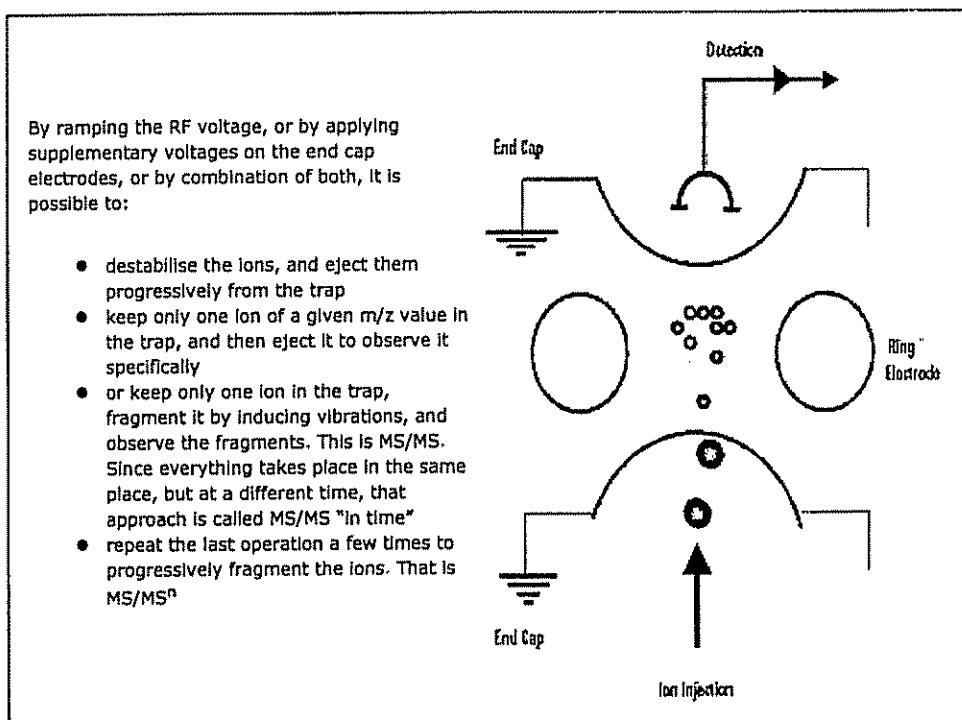
However, one should keep in mind that, when doing quantitation, the first important step is the ionisation, which takes place in the source. The presence of interfering compounds in the source might cause unexpected effects, like "ion suppression". Such effects impact the quantitation, whatever the M: analyser. Using an MS/MS system might reduce the problem, but does not eliminate it.

The Ion Trap Analyzer

This analyser is also known as the quadrupole ion trap analyser (QIT). It was first used on GC/MS instruments, then on LC/MS systems.

The principle of the trap is to store the ions in a device consisting of a ring electrode and two end cap electrodes. The ions are stabilized in the trap by applying a RF voltage on the ring electrode.

For maximum efficiency, the ions must be focussed near the centre where the trapping fields are closest to the ideal and the least distorted - maximizing resolution and sensitivity. This is achieved by introducing a damping gas (99.998% helium) that collisionally cools injected ions, damping down their oscillations until they stabilize.

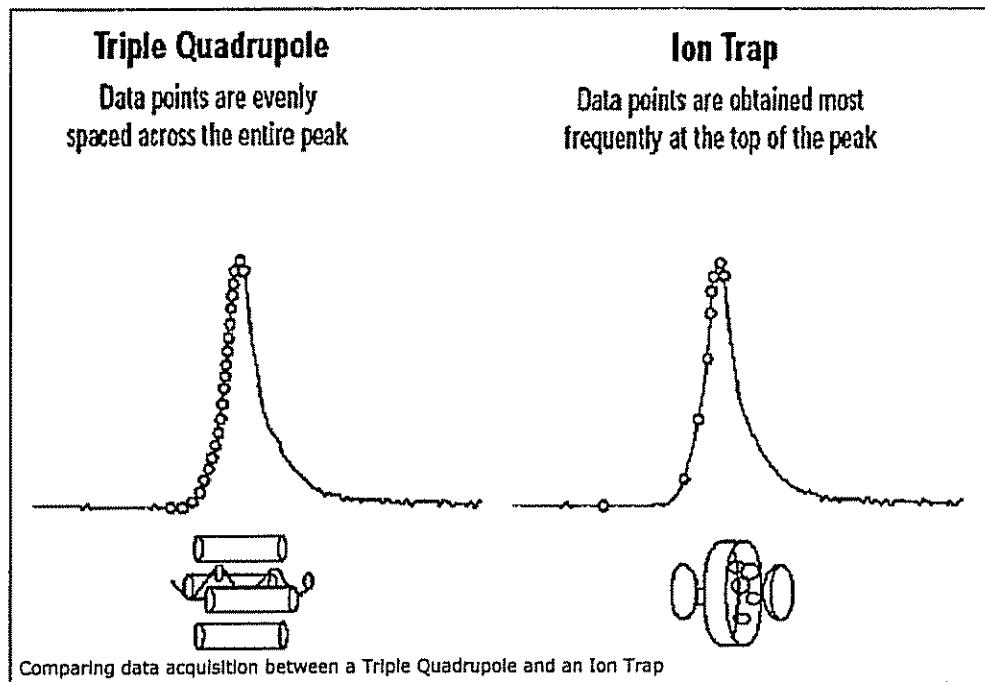


Resolution of the ion trap analyser: the resolution which is achievable with an ion trap depends upon the scan range and scan speed. When scanning over a few hundred Daltons in a fraction of a second, the typical resolution is similar to the resolution of a quadrupole. However, it is possible to increase the resolution by scanning at lower speed over a reduced mass range ("zoom scan"). In these conditions the resolution exceeds 5000 when scanning over a 10 Dalton window, which is sufficient to determine the number of charges of a multicharged small peptide.

Data acquisition: A typical acquisition cycle, for a trap used in MS mode, includes the following automated steps (from supplier literature)

1. Prescan: this is to determine the needed injection time : 60 ms
2. Ion injection: about 500 ms. This is the admission of the ions into the trap. The duration depends upon the signal intensity
3. Set the trap parameters for ion isolation, activation...: 80 ms
4. Mass Analysis: about 70 ms Additional steps are needed for MS/MS or MSⁿ operation

Additional steps are needed for MS/MS or MSⁿ operation



The ion trap is more sensitive in scan mode than in SIM mode.

Generally quadrupole instruments used in SIM mode provide an order of magnitude better limit of quantitation with lower relative standard deviations for quantitative experiments than an ion trap, primarily due to integration effect (more data points to determine the peak start and end with a quadrupole).

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Time of Flight (TOF) Analyser

This analyser is commonly called the TOF. The TOF is used in single MS systems, with an LC introduction with a GC introduction, or with MALDI ionisation. In MS/MS configuration, the TOF is associated to a quadrupole (QTof), or to another TOF (TOF-TOF) or to an Ion Trap (QIT/TOF).

Principle of the time of flight analyser: In a Time-Of-Flight (TOF) mass spectrometer, ions formed in an ion source are extracted and accelerated to a high velocity by an electric field into an analyser consisting of a long straight 'drift tube'. The ions pass along the tube until they reach a detector.

After the initial acceleration phase, the velocity reached by an ion is inversely proportional to its mass (strictly, inversely proportional to the square root of its m/z value).

Since the distance from the ion origin to the detector is fixed, the time taken for an ion to traverse the analyser in a straight line is inversely proportional to its velocity and hence proportional to its mass (strictly, proportional to the square root of its m/z value). Thus, each m/z value has its characteristic time-of-flight from the source to the detector.

Time of Flight equations: The first step is acceleration through an electric field (E volts). With the usual nomenclature (m = mass, z = number of charges on an ion, e = the charge on an electron, v = final velocity reached on acceleration), the kinetic energy ($mv^2/2$) of the ion is given by equation (1).

$$mv^2/2 = z.e.E \quad (1)$$

Equation (2) follows by simple rearrangement.

$$v = (2z.e.E/m)^{1/2} \quad (2)$$

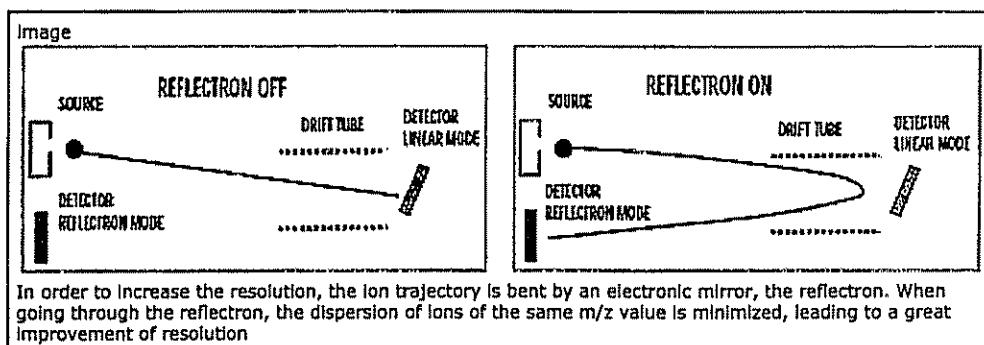
If the distance from the ion source to the detector is d , then the time (t) taken for an ion to traverse the drift tube is given by equation (3).

$$t = d/v = d/(2z.e.E/m)^{1/2} = d \cdot [(m/z)/(2e.E)]^{1/2} \quad (3)$$

In equation (3), d is fixed, E is held constant in the instrument and e is a universal constant. Thus, the flight time of an ion t is directly proportional to the square root of m/z (equation 4).

$$t = (m/z)^{1/2} \times \text{a constant} \quad (4)$$

Equation (4) shows that an ion of m/z 100 will take twice as long to reach the detector as an ion of m/z 25:



Characteristics of the time of flight analyser:

Mass range: there is no upper theoretical mass limitation; all ions can be made to proceed from source to detector and the upper mass limit exceeds 500 kDa. In practice, there is a mass limitation, in that it becomes increasingly difficult to discriminate between times of arrival at the detector as the m/z value becomes large. Another limitation is that very large molecules are difficult to ionise. Using an ionisation technique which produces multiply charged ions, like electrospray ionisation, extends the working range of the TOF analyser.

Resolution: with a TOF instrument, it is possible to obtain 10000 FWHM resolution

Mass accuracy: better than 5 ppm, using a reference mass; that allows unambiguous formula determination of small organic molecules

MALDI TOF, OA-TOF

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Two different sample introduction/ionisation techniques are used with time of flight analysers: MALDI and orthogonal acceleration.

oa-TOF: this is for in line coupling. This configuration is used for LC/MS with API ionisation, and for GC/MS. The ions are transferred from the source to the analyser through a transfer optics. The "pusher" accelerates the ions to the same level of energy, and gives the start signal for timing the flight.

QTOF

The QToF is a hybrid MS/MS instrument combining a quadrupole with a Tof analyser. This combination provides the benefits of in space MS/MS (selectivity, flexibility for collision experiments) with the advantages of the Tof (sensitivity in scan mode, fast scan, accurate mass, resolution). This is an ideal combination for sophisticated applications.

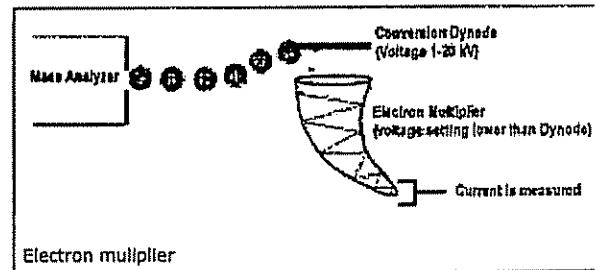
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Detectors

The detector is the device which detects the ions separated by the analyser. 3 different types of detectors are used with the analysers described in the previous pages: Electron multipliers, dynolyte photomultiplier, microchannel plates.

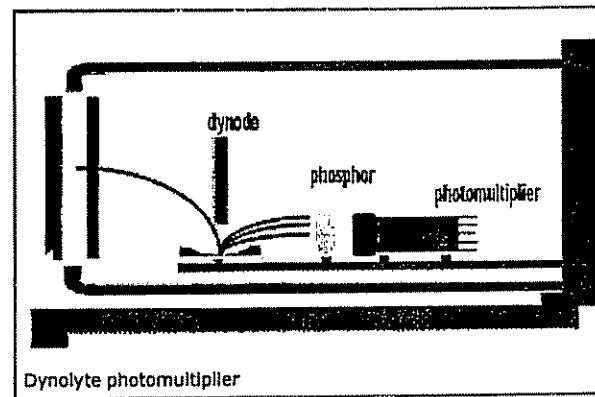
Electron multiplier

A conversion dynode is used to convert either negative or positive ions into electrons. These electrons are amplified by a cascade effect in a horn shape device, to produce a current. This device, also called channeltron, is widely used in quadrupole and ion trap instruments.



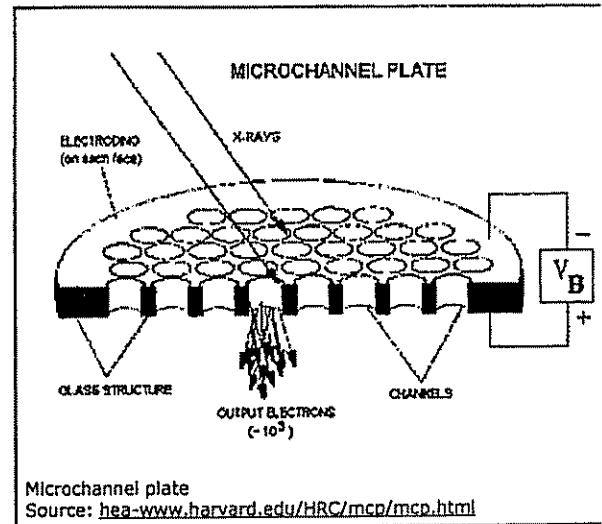
Dynolyte photomultiplier

Ions exiting the quadrupole are converted to electrons by a conversion dynode. These electrons strike a phosphor which when excited, emit photons. The photons strike a photocathode at the front of the photomultiplier to produce electrons and the signal is amplified by the photomultiplier. The photomultiplier is sealed in glass and held under vacuum. This prevents contamination and allows the detector to maintain its performance for a considerably longer period than conventional electron multipliers.



Microchannel plate

Most TOF spectrometers employ multichannel plate (mcp) detectors which have a time response < 1 ns and a high sensitivity (single ion signal > 50 mV). The large and plane detection area of mcp's results in a large acceptance volume of the spectrometer system. Only few mcp channels out of thousands are affected by the detection of a single ion i.e. It is possible to detect many ions at the same time which is important for laser ionisation where hundreds of ions can be created within a few nanoseconds. dynode phosphor photomultiplier.



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EXHIBIT R

United States Court of Appeals for the Federal Circuit

05-1172

NORIAN CORPORATION,

Plaintiff-Appellant,

v.

STRYKER CORPORATION,

Defendant-Appellee.

Brian M. Poissant, Jones Day, of New York, New York, argued for plaintiff-appellant. With him on the brief were Daniel L. Malone and Eric C. Stops.

Gregory J. Vogler, McAndrews, Held & Malloy, Ltd., of Chicago, Illinois, argued for defendant-appellee. With him on the brief were Timothy J. Malloy, Sandra A. Frantzen, and John L. Abramic.

Appealed from: United States District Court for the Northern District of California

Judge William H. Alsup

United States Court of Appeals for the Federal Circuit

05-1172

NORIAN CORPORATION,

Plaintiff-Appellant,

v.

STRYKER CORPORATION,

Defendant-Appellee.

DECIDED: December 6, 2005

Before NEWMAN, RADER, and BRYSON, Circuit Judges.

BRYSON, Circuit Judge.

This patent case comes before us for a second time. On the first appeal, we reversed the district court's grant of summary judgment of noninfringement, which we held was based on an unduly restrictive claim construction. Norian Corp. v. Stryker Corp., 363 F.3d 1321 (Fed. Cir. 2004). On remand, the district court again entered summary judgment of noninfringement based on its construction of a different claim limitation. Norian Corp. v. Stryker Corp., C.A. No. 01-00016 (WHA) (N.D. Cal. Dec. 3, 2004). We affirm.

I

The patent in suit, U.S. Pat. No. 6,002,065 ("the '065 patent"), is owned by appellant Norian Corporation. As the district court explained, the patent is directed to kits "for preparing rapidly setting calcium phosphate compositions to be used as 'bone cements' in medical or dental procedures." The asserted claims of the '065 patent are claims 8-10. Claim 8 provides as follows:

A kit for preparing a calcium phosphate mineral, said kit consisting of:

at least one calcium source and at least one phosphoric acid source free of uncombined water as dry ingredients; and

a solution consisting of water and a sodium phosphate, where the concentration of said sodium phosphate in said water ranges from 0.01 to 2.0 M and said solution has a pH in the range of about 6 to 11.

Dependent claim 9 recites the kit of claim 8 wherein the sodium phosphate is present in the water at a concentration ranging from about 0.05 to 0.5 M. Dependent claim 10 recites the kit of claim 8 wherein the solution has a pH in the range from about 7 to 9.

The issue before the district court was very narrow. It was undisputed that the accused kit sold by Stryker consisted of a vial of powdered material containing sources of calcium and phosphoric acid, a spatula, and a syringe filled with a 0.25 M sodium phosphate solution. The solution was made from two different sodium phosphates: monobasic sodium phosphate monohydrate and dibasic sodium phosphate heptahydrate. The question posed to the district court was whether Stryker's sodium phosphate solution was "a solution consisting of water and a sodium phosphate" within the meaning of that portion of claim 8. That question turned on whether the district court construed the claim term "a sodium phosphate" to include a solution prepared from one or more sodium phosphates, or whether the term was limited to a solution

prepared from only a single sodium phosphate. The district court concluded that the claim term required that the solution be made from only a single sodium phosphate. Because it was undisputed that Stryker's solution was made from more than one sodium phosphate, the court ruled that Stryker's solution did not infringe Norian's patent. Norian appeals, contending that the district court's claim construction was too narrow, and that the term "solution consisting of water and a sodium phosphate" should be construed to include solutions made from multiple sodium phosphates and should not be limited to solutions made from only a single sodium phosphate.

II

It is undisputed that there are multiple types of sodium phosphates. The '065 patent refers to several of them: monobasic sodium phosphate, which contains one sodium atom, two hydrogen atoms, and one phosphate group; dibasic sodium phosphate, which contains two sodium atoms, one hydrogen atom, and one phosphate group; and trisodium phosphate, which contains three sodium atoms and one phosphate group. Each of the sodium phosphates can be associated with different numbers of water molecules.

Norian argues that its claims read on any solution made from a single sodium phosphate as well as any solution made from a combination of different sodium phosphates. The claim term "a sodium phosphate," according to Norian, should be understood to embrace a mixture of multiple types of sodium phosphates as well as a single sodium phosphate. That construction makes sense, according to Norian, because once the various sodium phosphates are put into a water solution, they

dissociate into ions, and the same ions are present in the resulting solution regardless of which type or types of sodium phosphates were used as the starting materials.

The district court rejected Norian's argument on several grounds. First, the court noted that the asserted claims use the restrictive term "consisting of" to define the contents of the claimed solution. In that context, the court explained, the term "a" must be interpreted to mean that the solution consists of water and only a single solute, i.e., a single type of sodium phosphate, not a mixture of different sodium phosphates. The court found support for that interpretation in the specification, which contains repeated references to solutions made from a single sodium phosphate, but contains no reference to making the solution from more than one sodium phosphate. In addition, the court noted that claim 8 uses the phrase "at least one" in the first limitation, which refers to sources of calcium or phosphoric acid, but does not use that phrase in the second limitation, which refers to the ingredients of the solution. The court pointed to the use of the term "a" rather than the phrase "at least one" as indicating that only a single type of sodium phosphate is used in the claimed solution. Finally, the court ruled that the prosecution history of the '065 patent shows that the patentee surrendered the claim scope that was encompassed by the phrase "a sodium phosphate solution" in the predecessor to claim 8 when the patentee amended that language to read "a solution consisting of water and a sodium phosphate."

We agree with the district court's construction of the claim language. The patent contains multiple references to various different sodium phosphates. In that context, the reference in the claim to "a sodium phosphate" is most naturally understood as a reference to one of the different sodium phosphates. As the district court pointed out,

the language used to claim the solution in claim 8 is different from the formulation used in the same claim to describe the sources of calcium and phosphoric acid, where the claim refers to "at least one calcium source and at least one phosphoric acid source." If the patentee had meant to claim the use of at least one type of sodium phosphate in the recited solution, it would have been simple to use the same language in the second portion of the claim that was used in the first.

Even aside from the departure from the "at least one" phrase used in the first limitation, the word "a" is conspicuous in the phrase "a sodium phosphate." Although the word "a" generally means "one or more" in open-ended claims containing the transitional phrase "comprising," KCJ Corp. v. Kinetic Concepts, Inc., 223 F.3d 1351, 1356 (Fed. Cir. 2000), that general rule does not apply when the specification or the prosecution history shows that the term was used in its singular sense. See, e.g., Elkay Mfg. Co. v. Ebcо Mfg. Co., 192 F.3d 973, 977-79 (Fed. Cir. 1999) (noting that "our cases emphasize that 'a' or 'an' can mean 'one' or 'more than one,' depending on the context in which the article is used," and holding that the phrase "comprising . . . an upstanding feed tube" is limited to a single such feed tube based on the prosecution history); AbTox, Inc. v. Exitron Corp., 122 F.3d 1019, 1023-27 (Fed. Cir. 1997) (limiting the phrase "comprising . . . a metallic gas-confining chamber" to a single such chamber based on context gleaned from the specification). In particular, this court has interpreted the word "a" in its singular sense when, as in this case, it has been used in conjunction with the closed transitional phrase "consisting of." See Abbott Labs. v. Baxter Pharm. Prods., Inc., 334 F.3d 1274, 1281 (Fed. Cir. 2003) ("[A]lthough 'a' without more generally could mean one or more in an open-ended patent claim, 'a' with

'consisting of' in this case indicates only one member of a Markush group."). Thus, the claim language "consisting of . . . a sodium phosphate," on its own, suggests the use of a single sodium phosphate.

That interpretation is consistent with the specification, as the district court ruled. In particular, example 3 of the specification includes a chart listing the different setting times that are associated with different solutions. Each of the listed solutions contains a single solute, which is either a type of sodium phosphate or a type of sodium carbonate. While the scope of a claim is not necessarily limited to the examples disclosed in the specification, nothing in the '065 patent specification points away from the district court's construction limiting claim 8 to single-solute solutions. Rather, each of the solutions described in the specification uses only a single solute, and the specification makes no reference to using a mixture of multiple solutes in a single solution.

Norian has argued that the specification contains references to solutions made from multiple types of sodium phosphates. In reissue proceedings before the Patent and Trademark Office, Norian argued that example 3 mentions a solution made from a mixture of trisodium phosphate dodecahydrate and dibasic sodium phosphate heptahydrate. '065 patent col. 10, ll. 46-50. However, as the PTO pointed out, that solution is not the solution recited in claim 8, but instead is a "colloid control" used in connection with the claimed solutions described in example 3. Norian also argues that example 2 supports its claim construction through its reference to "Sigma Diagnostics 1.0 M Phosphate Buffer," an "off the shelf" buffer solution. '065 patent, col. 9, ll. 52-59. Norian contends that off-the-shelf buffer solutions are made from mixtures of multiple types of sodium phosphates. However, the trial court concluded based on the evidence

of record that Sigma's phosphate buffer solution was made from potassium phosphates, not sodium phosphates, and that the use of the term "phosphate buffer" does not imply that the buffer solution was made from multiple forms of sodium phosphates, or even any sodium phosphates at all. Thus, nowhere in the specification does the patentee refer, either explicitly or implicitly, to making the claimed solution from a mixture of multiple sodium phosphates.

The district court was also correct to rely on the prosecution history, which reflects a series of patentability rejections, followed by narrowing amendments and clarifying explanations from the prosecuting attorney. The prosecution history shows that through the series of amendments, Norian surrendered significant scope for what became claim 8. In response to one series of rejections, Norian narrowed the claim by changing the transitional phrase in the claim's preamble from "comprising" to "consisting essentially of" and then ultimately to "consisting of." In response to another rejection, Norian amended the critical claim language by replacing the words "a sodium phosphate solution" with the words "a solution consisting of water and a sodium phosphate." The prosecuting attorney advised the examiner that the amendment "limit[ed] the claimed kit to one in which the solution is made of water and a single solute, where the solute is either a sodium phosphate or a sodium carbonate, which solute is completely dissolved in the water" (emphasis added).

If there were any doubt that the reference to "a sodium phosphate" meant a single type of sodium phosphate, the prosecuting attorney directed the examiner to the specification's tables for examples of the single-solute solutions to which the amended claim was limited. As the prosecuting attorney noted, the tables disclose "solutions of

different sodium phosphates": one solution is made from monobasic sodium phosphate, another from dibasic sodium phosphate, and a third from trisodium phosphate. But none of the solutions is made from a mixture of different sodium phosphates. In other words, the specification contemplates the use of various forms of sodium phosphate, but used individually, not simultaneously in the same solution. As the prosecuting attorney explained, the claim was limited "with the incorporation of the additional limitation limiting the solution to one that consists of water and a sodium phosphate."

Other references in the prosecution history underscore the restrictive scope that was accorded to the claim language. Thus, the prosecuting attorney explained that "the solution is limited to one that is made of water and a solute selected from a sodium phosphate or sodium carbonate," and that "the claimed kits of the present application are limited to kits in which the setting liquid is a solution of water and a solute, where the solute is either a sodium phosphate or a sodium carbonate." The district court properly construed that language to limit the scope of the claim at issue in this case to a single solute in the water solution, i.e., to a single type of sodium phosphate.

Norian makes essentially three arguments in response to the district court's claim construction. First, Norian argues that after any sodium phosphate salt goes into solution, it does not maintain its solid, compound form, and thus it ceases to be identifiable as, for example, monobasic sodium phosphate monohydrate or dibasic sodium phosphate heptahydrate. Instead, it dissolves into dissociated sodium ions and phosphate ions in water. Therefore, according to Norian, the reference to "a sodium phosphate" in a water solution can only mean a solution containing sodium ions and

phosphate ions, which solution will be produced when any one or more types of sodium phosphates are added to water.

The problem with that argument is that it runs afoul of the language and the prosecution history of the '065 patent. In the claim language, the specification, and the prosecution history, the patentee described the claimed solution by reference to the substances used to make it—solutes that include a variety of different types of sodium phosphates. The patentee could have chosen to claim the solution as "a sodium phosphate solution," as was recited in an earlier version of the claims, or as a solution consisting of "at least one sodium phosphate," which would have tracked the language used in the first limitation of claim 8. Instead, the patentee departed from those formulations and chose to recite a solution consisting of water and "a sodium phosphate." In context, that language denotes a solution made from water and a single solute drawn from among the various types of sodium phosphates.

Norian's second argument is that the prosecution history cannot be read as broadly as the district court read it. Norian explains that the amendment in question (i.e., amending the language from "a sodium phosphate solution" to "a solution consisting of water and a sodium phosphate") was made in response to a prior art patent to Iwamoto, which disclosed a colloidal setting solution, rather than a pure solution containing no suspended particles. Because the sole purpose of the amendment was to avoid the effect of the Iwamoto reference, Norian argues, the prosecution history should not be interpreted as disclaiming pure solutions that are made from more than a single solute.

The problem with that argument is that there is no principle of patent law that the scope of a surrender of subject matter during prosecution is limited to what is absolutely necessary to avoid a prior art reference that was the basis for an examiner's rejection. To the contrary, it frequently happens that patentees surrender more through amendment than may have been absolutely necessary to avoid particular prior art. In such cases, we have held the patentees to the scope of what they ultimately claim, and we have not allowed them to assert that claims should be interpreted as if they had surrendered only what they had to. See, e.g., Fantasy Sports Props., Inc. v. Sportsline.com, Inc., 287 F.3d 1108, 1114-15 (Fed. Cir. 2002) (patentee "cannot now be heard to argue" a broad construction of the term "bonus points" because patentee acquiesced in the examiner's narrow interpretation to distinguish the claims from prior art, even though under the broad construction the invention may have been patentably distinct from the prior art); Elkay Mfg. Co., 192 F.3d at 979 (patentee relinquished a construction of claim language that could include separate air and liquid feed tubes, because patentee distinguished a prior art reference by arguing that the reference taught the use of separate liquid and air feed tubes; court found it "irrelevant . . . whether [patentee] had to relinquish an interpretation of the feed tube limitation that could cover more than one flow path for liquid and air"). Here, in the course of amending, the patentee expressly spoke to the meaning of the amended claim, noting that it was limited to a single solute. We therefore agree with the district court that Norian surrendered all sodium phosphate solutions made from more than a single solute, i.e., a single type of sodium phosphate.

Norian's third argument is that by defining the solution of the asserted claims in terms of the ingredients used to make the solution, rather than in terms of the ions found in the solution after it was made, the court has improperly converted what was meant to be a product claim into a product-by-process claim, without applying the legal principles applicable to such claims. We disagree. All that the district court has done is to conclude that the patentee characterized the solution in terms of the components put into it, which the evidence before the court (including the specification) showed to be a conventional means of describing a solution. Because the patentee chose to describe the solution in that fashion, the claims remained product claims, but their scope was limited to the designated ingredients from which the claimed solution was made.

Ultimately, Norian's arguments distill to the basic contention that a person of skill in the art would understand that any "sodium phosphate solution" will contain sodium ions and phosphate ions, no matter whether it is made from one type or multiple types of sodium phosphate. While that may be so, it does not change the clear effect of the prosecution history, the specification, and the claim language. Rheox, Inc. v. Entact, Inc., 276 F.3d 1319, 1320-21 (Fed. Cir. 2002) (holding that the term "calcium orthophosphate," as used in the claim and in light of the prosecution history, did not cover monocalcium orthophosphate, even though a person of skill in the art would recognize that the term generally refers to a family of compounds that includes monocalcium orthophosphate). Norian did not simply claim a "sodium phosphate solution"; nor did Norian broadly claim a solution containing sodium and phosphate ions. Instead, Norian limited the solution in claim 8 to one using a single type of sodium phosphate. Although Norian might have claimed the solution more broadly, it did not,

and we are not now free to interpret the claim in a way that is at odds with the claim language and other intrinsic evidence.

Finally, Norian argues that even if the district court was correct in its claim construction and literal infringement was not established, the court still should not have foreclosed its effort to prove infringement under the doctrine of equivalents. Norian, however, amended the pertinent claim language in a way that, as the district court construed it, disclaimed solutions made from multiple types of sodium phosphates. If the district court was correct in that characterization of the prosecution history—and we believe that it was—Norian is not entitled to prevail on a doctrine of equivalents theory. Instead, under the doctrine of prosecution history estoppel, a narrowing of claim scope during prosecution creates a presumption that the patentee has surrendered, for purposes of the doctrine of equivalents, all subject matter falling between the scope of the original claim and the scope of the claim as amended. See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 741 (2002).

Norian does not suggest that this case falls within one of the exceptions to the rule of prosecution history estoppel set forth by the Supreme Court in Festo. See Festo, 535 U.S. at 740-41. Instead, Norian's argument is that Festo is inapplicable altogether because Norian never surrendered the subject matter in dispute. As indicated above, we have rejected Norian's interpretation of the prosecution history, and we have concluded, contrary to Norian's argument, that the patentee disclaimed solutions made from more than one form of sodium phosphate. As such, Festo is applicable to Norian's argument under the doctrine of equivalents, and in the absence of any suggestion of why the principles of Festo do not bar Norian from recourse to that doctrine to establish

infringement, we hold that Norian cannot avoid summary judgment of noninfringement on that ground. Accordingly, we uphold the district court's judgment in all respects.

AFFIRMED.

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CERTIFICATE OF SERVICE

I hereby certify that on December 15, 2005, I electronically filed the foregoing document with the Clerk of Court using CM/ECF which will send notification of such filing, and hand delivered, to the following:

Josy W. Ingersoll
Adam W. Poff
Young, Conaway, Stargatt & Taylor, LLP
The Brandywine Building, 17th Floor
1000 West Street
Wilmington, DE 19899

I hereby certify that on December 15, 2005, I sent the foregoing document by Federal Express to the following non-registered participants:

Walter E. Hanley, Jr.
James Galbraith
Huiya Wu
Kenyon & Kenyon
One Broadway
New York, NY 10004

William G. James, II
Fred T. Grasso
Kenyon & Kenyon
1500 K Street N.W., Suite 700
Washington, DC 20036

Kelly E. Farnan
Kelly E. Farnan (#4395)
(Farnan@RLF.com)

DATED: December 15, 2005

CERTIFICATE OF SERVICE

I hereby certify that on December 22, 2005, I electronically filed the foregoing document with the Clerk of Court using CM/ECF which will send notification of such filing, and hand delivered, to the following:

Josy W. Ingersoll
Adam W. Poff
Young, Conaway, Stargatt & Taylor, LLP
The Brandywine Building, 17th Floor
1000 West Street
Wilmington, DE 19899

I hereby certify that on December 22, 2005, I sent the foregoing document by Federal Express to the following non-registered participants:

Walter E. Hanley, Jr.
James Galbraith
Huiya Wu
Kenyon & Kenyon
One Broadway
New York, NY 10004

William G. James, II
Fred T. Grasso
Kenyon & Kenyon
1500 K Street N.W., Suite 700
Washington, DC 20036

Kelly E. Farnan
Kelly E. Farnan (#4395)
(Farnan@RLF.com)

DATED: December 22, 2005